Equipoise: Where does it stand in current clinical research

Saumya Panda, Anupam Das[1]

Department of Dermatology, Belle Vue Clinic, [1]Department of Dermatology, KPC Medical College and Hospital, Kolkata, West Bengal, India

Equipoise is defined as a state of professional uncertainty about the relative therapeutic merits of treatments provided to patients. The principle of equipoise states that if there is uncertainty or conflicting expert opinion about the relative therapeutic, prophylactic or diagnostic merits of a set of interventions, it is permissible to allocate a participant to receive an intervention from this set, so long as there is no consensus that an alternative intervention would better advance the participant's interests.

Benjamin Freedman shaped the important concept of clinical equipoise. In operational terms, clinical equipoise is represented by the treatment arms in a controlled clinical trial.[1] It has also been called an honest null hypothesis and/or an uncertain state.

However, equipoise questions the ethical legitimacy of randomized clinical trials (RCTs), and the promotion of premature discontinuation of trials based on interim data relating to treatment benefit. If equipoise is to be followed, trials should be abruptly terminated when equipoise gets disturbed. However, such untimely termination generates erroneous interpretations in decision-making in health policies.[2] It has been observed that there is an increasing incidence of early termination of randomized clinical trials, leading to an undue overestimation of benefits associated with treatment.[3] Moreover, early and untimely discontinuation of a clinical trial makes it difficult to assess the chances of the development of adverse effects associated with a treatment. Equipoise has an unavoidable tendency to bias the evidence base with respect to risk-benefit assessment and it allows randomization even when individual clinicians are not uncertain about how best to treat a patient.

Equipoise narrowly locates the ethical concern about trials within the orbit of the doctor-patient relationship. The proponents of equipoise have characterized RCTs solely as tools to guide clinicians in decision-making about medical care. This "therapeutic orientation" to clinical research ignores the wider societal interest in evidence-based health policy, as reflected in regulatory decisions to approve new treatments for licensing, something that should resonate deeply during this COVID-19 pandemic that we are passing through.

In situations of life and death, expedited evaluation of all potentially beneficial therapies can only occur with a commitment by all stakeholders to subscribe to the fundamental tenets of evidence-based medicine. At best, completion of randomized clinical trials may permit expansion of novel therapies among new patient populations. At worst, additional uncontrolled observational reports will prolong the uncertainty. Physicians, patients, regulators and industry must work together to move beyond equipoise.

If equipoise is to be discarded, we have to design studies to generate information, with an aim to resolve the uncertainty and reduce the divergence in opinion among qualified medical experts. Moreover, if we intend to expose the participants to any risk arising out of the study, it should be comparable enough with regard to the quantum of scientific information the study is likely to provide. Study participants must be explained (during informed consent process) about the nature of uncertainty associated with the intervention during the study and that their willingness to participate in the study is going to improve the state of medical care.

Therefore, clinical equipoise is an assumption that there is not one 'better' intervention present (for either the control or experimental group) during the design of a randomized controlled trial; and this is a necessary ingredient to conduct a truly unbiased RCT.

Until 2004 when the first biologic was approved by the United States Food and Drug Administration (USFDA) for

How to cite this article: Panda S, Das A. Equipoise: Where does it stand in current clinical research. Indian J Dermatol Venereol Leprol 2022;88:135-6.

Corresponding author: Anupam Das, Department of Dermatology, KPC Medical College and Hospital, Kolkata, West Bengal, India. anupamdasdr@gmail.com

Received: December, 2020 **Accepted:** October, 2021 **EPub Ahead of Print:** November, 2021 **Published:** February, 2022

DOI: 10.25259/IJDVL_1163_20 **PMID:** 34877839

psoriasis, the therapy was full of dilemma and uncertainty. But, with the availability of numerous molecules (including biologics), placebo-controlled trials no longer continue to meet the ethical standard of clinical equipoise. As per recent guidelines, all biologics have been recommended as monotherapy for adults with moderate-to-severe plaque psoriasis, which indirectly means that if patients are provided placebo treatment in a clinical trial, we are providing them substandard care, i.e., placebo-controlled trials for psoriasis do not maintain clinical equipoise anymore. Moreover, it also means that we should now shift from placebo-controlled trials to active comparison trials with an existing biologic, in order to ensure ethical appropriateness of the trial.[4]

Two different interventions in a trial may have significant difference in terms of onset of action and adverse effect profile. Therefore, it is not prudent to conclude the superiority of an intervention based on interim results. Since most dermatoses are chronic, factors like effectiveness, safety, tolerability, rate of relapse and recurrence are important while judging the superiority of one intervention, e.g., choice of therapeutic agent for a patient of psoriasis depends on adverse effect profile, profession, comorbidities, lifestyle and the rapidity of the expected therapeutic response. Phototherapy can be a better choice for an alcoholic patient who cannot be prescribed hepatotoxic drugs. However, cyclosporine may be preferred in patients who want a rapid response. Similarly, methotrexate and acitretin may be better options in patients with otherwise normal hematological parameters.

Dermatology is a medical subspeciality with a rapidly enlarging scope of surgical interventions. Thus, dermatologists must get themselves acquainted with "time until treatment equipoise" to advise patients of relative risks of the two approaches. This is defined as the duration of time that elapses after a surgical intervention before the risk of the intervention is nullified and reversed by the cumulative risk of conservative management.[5] This concept is helpful in developing treatment algorithms for conditions such as vitiligo, melasma or sundry other diseases where there are competing medical and surgical modes.

In a nutshell, equipoise remains a highly debated concept in clinical research. Miller and Brody found the concept so flawed as to give a call to banish it altogether from research.[6] Others aver that although personal equipoise is elusive, acceptance of clinical equipoise is well within reason. On the moral compass of scientific research, equipoise represents a polar position, providing a framework of ethical principles and research integrity beyond reproach. In order to recognize and uphold equipoise, researchers must be trained and encouraged to recognize, appreciate and root out biases in their work. The alternative will be to accept research fraud of all kinds that are only too visible and frequent these days.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987;317:141-5.
2. Chiong W. Equipoise and the dilemma of randomized clinical trials. N Engl J Med 2011;364:2077.
3. Bassler D, Briel M, Montori VM, Lane M, Glasziou P, Zhou Q, *et al*. Stopping randomized trials early for benefit and estimation of treatment effects: Systematic review and meta-regression analysis. JAMA 2010;303:1180-7.
4. Nguyen C, Housholder A, Fleischer A. Is the concept of clinical equipoise maintained in psoriasis research? J Dermatolog Treat 2020;31:1.
5. Noorani A, Hippelainen M, Nashef SA. Time until treatment equipoise: A new concept in surgical decision making. JAMA Surg 2014;149:109-11.
6. Miller FG, Brody H. Clinical equipoise and the incoherence of research ethics. J Med Philos 2007;32:151-65.